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(57) Abstract

A method for treating urinary incontinence while avoiding concomitant liability of adverse effects associated with racemic oxybutynin is disclosed. The method comprises administering from 100 mg to 1 000 mg/day of (S)-oxybutynin, (S)-desethyloxybutynin or a pharmaceutically acceptable salt thereof, substantially free of the corresponding R enantiomer. Pharmaceutical compositions in the form of tablets, soft elastic gelatin capsules and transdermal devices comprising an acceptable carrier and up to 500 mg of (S)-oxybutynin or (S)-desethyloxybutynin are also disclosed.

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TREATING URINARY INCONTINENCE USING (S)-OXYBUTYNIN AND (S)-DESETHYLOXYBUTYNIN

FIELD OF THE INVENTION

The invention relates to a method and dosage forms for treating urinary incontinence using optically pure (S)-oxybutynin (S-OXY) and (S)-desethyloxybutynin (S-DEO).

BACKGROUND OF THE INVENTION

Racemic oxybutynin (OXY) is used therapeutically in the treatment of intestinal hypermotility and in the treatment of urinary incontinence due to detrusor instability. Racemic oxybutynin exerts a direct antispasmodic effect on smooth muscle and inhibits the action of acetylcholine on smooth muscle. It exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. It is quite selective for muscarinic receptors in the presence of nicotinic receptors and as a result, no blocking effects are observed at skeletal neuromuscular junctions or autonomic ganglia.

Racemic oxybutynin relaxes bladder smooth muscle and, in patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that racemic oxybutynin increases vesicle capacity, diminishes the frequency of involuntary contractions of the detrusor muscle, and delays the initial desire to void. It is therefore useful in the treatment and prevention of both incontinency and frequent voluntary urination. The efficacy of racemic oxybutynin in the bladder has been attributed to a combination of antimuscarinic, direct spasmolytic and local anesthetic effects on the detrusor smooth muscle. Because of the antimuscarinic activity of the racemic drug, xerostomia (dry mouth) and mydriasis (dilated pupils), which involve muscarinic cholinergic receptors, are very common side effects. In fact, at least one researcher has referred to the "inevitable symptoms of mydriasis, xerostomia, tachycardia, etc." that accompany the administration of racemic oxybutynin [Lish et al. Arch. Int. Pharmacodyn. 156, 467-488 (1965), 481]. The high incidence of anticholinergic side effects (40 to 80%) often results in dosage reduction or discontinuation of therapy.

Pharmacological studies of the individual enantiomers have suggested that the R-enantiomer is the efficacious enantiomer. Noronha-Blob et al. [J. Pharmacol. Exp. Ther. 256, 562-567 (1991)] concluded that the cholinergic antagonism of racemic oxybutynin (measured *in vitro* by its affinity for M_1, M_2 and M_3 receptors subtypes and *in vivo* for diverse physiological responses) could be attributed mainly to the activity of the (R)-enantiomer. For all responses they found the rank order of potency of racemic oxybutynin and its enantiomers to be the same, namely, (R)-oxybutynin greater than or equal to racemic oxybutynin, which was much greater than (S)-oxybutynin, with (S)-oxybutynin being 1 to 2 orders of magnitude less potent than (R)-oxybutynin.

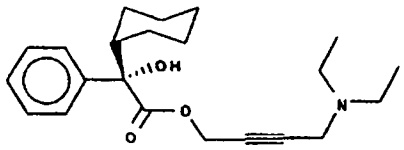
SUMMARY OF THE INVENTION

It has now been unexpectedly found that the substantially optically pure (S)-enantiomer of oxybutynin and of its desethyl metabolite provide a superior therapy for the treatment of urinary incontinence.

Optically pure (S)-oxybutynin (S-OXY) and (S)-desethyloxybutynin (S-DEO) provide this treatment while substantially reducing the adverse effects that primarily arise from anticholinergic activity and that are associated with the administration of racemic oxybutynin. These include, but are not limited to, xerostomia, mydriasis, drowsiness, nausea, constipation, palpitations and tachycardia. The amelioration of cardiovascular side effects of racemic oxybutynin, such as tachycardia and palpitations, by the administration of (S)-oxybutynin or S-DEO is of particular therapeutic value.

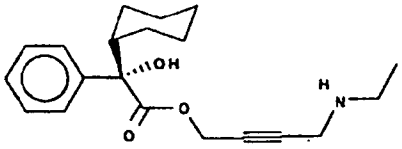
The active compounds of these compositions and methods are optical isomers of oxybutynin and desethyloxybutynin. The preparation of racemic oxybutynin is described in British Patent Specification 940,540. Chemically, the active compounds are (1) the S enantiomer of 4-(diethylamino)-2-butynyl α-cyclohexyl-α-hydroxybenzeneacetate also known as 4-(diethylamino)-2-butynyl phenylcyclohexylglycolate, and hereinafter referred to as oxybutynin; and (2) the S enantiomer of 4-(ethylamino)-2-butynyl α-cyclohexyl-α-hydroxybenzeneacetate, and hereinafter referred to as desethyloxybutynin. The generic name given to the hydrochloride salt of racemic oxybutynin by the USAN Council is oxybutynin chloride; it is sold under the trade name of Ditropan®.

The isomer of oxybutynin having the S absolute stereochemistry (Registry Number 119618-22-3) is dextrorotatory, and is shown in Formula I:



I

The S enantiomer of desethyloxybutynin is shown in Formula II:



II

The synthesis of (S)-oxybutynin has been described [Kachur et al. J. Pharmacol. Exp. Ther. 247, 867-872 (1988)], but (S)-oxybutynin itself is not presently commercially available. All of the clinical results that have been reported have been obtained with the racemic mixture, although the pharmacology of the individual enantiomers has been described in guinea pigs and rats [see Kachur et al. J. Pharmacol. Exp. Ther. 247, 867-872 (1988) and Noronha-Blob et al. J. Pharmacol. Exp. Ther. 256, 562-567 (1991)]. The synthesis and pharmacology of (S)-desethyloxybutynin has been described by us in PCT application WO 96/23492.

In one aspect the invention relates to a method for treating urinary incontinence while avoiding concomitant liability of adverse effects, which comprises administering to a human in need of such treatment a therapeutically effective amount of (S)-oxybutynin, (S)-desethyloxybutynin or a pharmaceutically acceptable salt of either, substantially free of the corresponding R enantiomer.

In another aspect, the present invention provides pharmaceutical compositions which comprise (S)-oxybutynin, (S)-desethyloxybutynin, or a pharmaceutically

acceptable salt of either, substantially free of its (R)-enantiomer, and a pharmaceutically acceptable carrier. The terms "substantially free of its R enantiomer" and "substantially free of the corresponding R enantiomer" as used herein mean that the compositions contain at least 90% by weight of (S)-oxybutynin or (S)-desethyloxybutynin and 10% by weight or less of (R)-oxybutynin or (R)-desethyloxybutynin, respectively. In a more preferred embodiment, the compositions contain at least 99% by weight of the S enantiomer and 1% or less of the R enantiomer.

The substantially optically pure (S)-oxybutynin or (S)-desethyloxybutynin may be administered parentally, rectally, intravesically, transdermally, orally or by aerosol. Oral and transdermal administration are preferred, at a rate of about 0.1 mg to about 1 gram per day.

In another aspect, the invention relates to a pharmaceutical unit dosage form in the form of a tablet, soft elastic gelatin capsule or a transdermal delivery device, comprising a therapeutically effective amount of (S)-oxybutynin, (S)-desethyloxybutynin or a pharmaceutically acceptable salt of either, substantially free of the corresponding R stereoisomer, and a pharmaceutically acceptable carrier. The tablet and soft elastic gelatin capsule forms may be prepared by conventional methods, well-known in the art, and the amount of (S)-oxybutynin, (S)-desethyloxybutynin or a pharmaceutically acceptable salt of either present in each unit dosage is preferably from about 0.1 mg to 500 mg, more preferably from about 25 mg to 250 mg, and even more preferably from about 100 mg to 200 mg. Transdermal administration is improved by the inclusion of a permeation enhancer in the transdermal delivery device.

DETAILED DESCRIPTION OF THE INVENTION

The S enantiomers of oxybutynin and DEO may be obtained by resolution of the intermediate mandelic acid followed by esterification. The esterification can be carried out as described by Kachur et al. (op. cit.) for OXY or by the improved method described in PCT application WO 96/23492. Alternatively, the S enantiomers of OXY and DEO may be obtained by the resolution of racemic oxybutynin or DEO using conventional means such as fractional crystallization of diastereomeric salts with chiral acids. Other

standard methods of resolution known to those skilled in the art, including, but not limited to, simple crystallization and chromatography on a chiral substrate can also be used.

The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr J. Chem. Ed. 62, 114-120 (1985). Thus, solid and broken wedges (such as shown in formula I) are used to denote the absolute configuration of a chiral element; wedge outlines and dotted or broken lines denote enantiomerically pure compounds of indeterminate absolute configuration.

The magnitude of a prophylactic or therapeutic dose of (S)-oxybutynin or S-DEO in the acute or chronic management of disease will vary with the severity and nature of the condition to be treated and the route of administration. The dose and perhaps the dose frequency will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range for (S)-oxybutynin or S-DEO for the conditions described herein is from about 0.1 mg to about 1 gram, preferably from about 0.4 mg to about 600 mg, more preferably from about 100 mg to about 1 g, even more preferably from about 240 mg to about 750 mg, and most preferably from 300 to 600 mg in single or preferably, divided doses. In managing the patient, the therapy should be initiated at a lower dose, perhaps at about 80 mg, and increased depending upon the patient's global response, *e.g.*, up to about 600 mg/day.

It is further recommended that patients over 65 years and those with impaired renal or hepatic function initially receive low doses and that they be titrated based on individual response(s) and blood level(s). It may be necessary to use dosages outside these ranges in some cases, as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response. The terms "a therapeutically effective amount" and "an amount sufficient to treat incontinence but insufficient to cause adverse effects" are encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of (S)-oxybutynin or S-DEO. For example, oral, rectal, parenteral (subcutaneous, intramuscular, intravenous), transdermal, aerosol and like forms of administration may be employed. Additionally, the drug may be administered directly

into the bladder through the urethra, as described for racemic oxybutynin by Massad et al. [J. Urol. 148, 595-597 (1992)]. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, transdermal delivery systems, and the like.

The pharmaceutical compositions of the present invention comprise (S)-oxybutynin or S-DEO as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic acids. Suitable pharmaceutically acceptable acid addition salts for the compound of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, and the like. The hydrochloride has particular utility and was, in fact, the salt used in the studies described below.

The compositions of the present invention include suspensions, solutions, elixirs, or solid dosage forms. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred over the oral liquid preparations. Because of their case of administration, tablets and capsules represent one of the more advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In a preferred embodiment, the pharmaceutical compositions of the present invention may be formulated in a soft elastic gelatin capsule unit dosage form by using conventional methods, well-known in the art (*see, e.g.*, Ebert, Pharm. Tech., 1(5):44-50(1977)). Soft elastic gelatin capsules have a soft, globular, gelatin shell somewhat thicker than that of hard gelatin capsules, wherein a gelatin is plasticized by the addition of glycerin, sorbitol or a similar polyol. The hardness of the capsule shell may be changed by varying the type of gelatin and the amounts of platiciser and water. The soft gelatin shells may contain a preservative to prevent the growth of fungi, such as methyl-

and propylparabens and sorbic acid. The active ingredient may be dissolved or suspended in a liquid vehicle or carrier, such as vegetable or mineral oils, glycols such as polyethylene glycol and propylene glycol, triglycerides, surfactants such as polysorbates, or a combination thereof. In the soft elastic gelatin capsule pharmaceutical unit dosage form of the present invention, (S)-oxybutynin or (S)-desethyloxybutynin is preferably present in an amount of about 0.1 mg to about 500 mg, more preferably in an amount of about 25 mg to about 250 mg, and even more preferably in an amount of about 100 mg to 200 mg.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by other controlled release means and delivery devices known to those of skill in the art.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of the active ingredient, as a powder or granules, or as soft elastic gelatin capsules wherein the active ingredient is dissolved or suspended in a liquid carrier, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation, just as is known for the racemic mixture.

The surprising utility of the (S)-enantiomer of both OXY and DEO has been established by the following studies.

ENANTIOMERS OF OXYBUTYNIN

Binding of (R)- and (S)-Oxybutynin to Human M_1, M_2, M_3 and M_4 Muscarinic Receptor Subtypes

Protein Source

The experiments were carried out on membranes prepared from SF9 cells infected with baculovirus to express the human recombinant M_1, M_2, M_3 and M_4 muscarinic receptor subtypes.

Binding Assays

Table 1

Receptor	Radioligand	Conc.	Nonspecific	Incubation	Reference Compound
M_{1H}	[^{3}H]pirenzepine	2nM	atropine (1μM)	60 min 27°C	pirenzepine
M_{2H}	[^{3}H]AF-DX 384	2nM	atropine (1μM)	60 min 27°C	methoctramine
M_{3H}	[^{3}H]4-DAMP	0.8nM	atropine (1μM)	60 min 27°C	4-DAMP
M_{4H}	[^{3}H]4-DAMP	0.3nM	atropine (1μM)	60min 27°C	4-DAMP

Following incubation, the assays were rapidly filtered under vacuum through GF/B glass fiber filters (Whatman) and washed with an ice-cold buffer using a Brandel Cell Harvester. Bound radioactivity was determined with a liquid scintillation counter (LS 6000, Beckman) using a liquid scintillation cocktail (Formula 99, DuPont NEN).

Experimental Protocol

The compounds were tested on each receptor at 10 concentrations in duplicate to obtain competition curves. In each experiment, the reference compound for the receptor under investigation was simultaneously tested at 8 concentrations in duplicate to obtain a competition curve in order to validate this experiment.

Analysis and expression of results

The specific radioligand binding of each receptor was defined as the difference between total binding and nonspecific binding determined in the presence of an excess of unlabeled ligand. IC_{50} values (concentrations required to inhibit 50% of specific binding)

were determined by non linear regression analysis of the competition curves. These parameters were obtained by curve fitting using Sigmaplot™ software. IC_{50} for R- and S-OXY are given in Table 2.

Table 2

Binding of R-oxybutynin and S-oxybutynin to human muscarinic subtypes M1 - M4

Receptor	R-OXY IC_{50}(nM)	S-OXY IC_{50}(nM)	Ref. Compound IC_{50}(nM)
M1	0.99	47.6	Pirenzepine 11.9
M2	9.9	178	Methoctramine 14.6
M3	1.8	149	4-DAMP 1.6
M4	1.2	100	4-DAMP 0.87

These results indicate that S-OXY has less affinity for muscarinic receptor subtypes than does R-OXY.

Binding of (R)- and (S)-Oxybutynin to Calcium Channels

Binding assays

Binding assays were performed using the following methods:

Table 3

Receptors	Membranes	Reference Compounds	References
Ca channel (T+L, diltiazem site)	rat cerebral cortex	diltiazem	Schoemaker and Langer (1985)
Ca channel (T+L, verapamil site)	rat cerebral cortex	D600	Reynolds et al (1986)

The experiment conditions were:

Table 4

Receptors	Ligands	Concentrations	Nonspecific	Incubation
Ca channel (T+L, diltiazem site)	[^{3}H] diltiazem	5nM	dilitiazem (10µM)	120 min 25°C
Ca channel (T+L,verapamil site)	[^{3}H]D 888	0.5 nM	D 600 (10µM)	60 min 22°C

Following incubation, the assays were rapidly filtered under vacuum through GF/B or GF/C glass fiber filters (Whatman) and washed with an ice-cold buffer using a Brandel Cell Harvester. Bound radio-activity was determined with a liquid scintillation counter (LS6000, Beckman) using a liquid scintillation cocktail (Formula 989, DuPont NEN).

Experimental Protocols

The compounds were tested in duplicate on each receptor at a concentration of 10^{-5}M. In each experiment, the reference compound for the receptor under investigation was simultaneously tested at 8 concentrations in duplicate to obtain a competition curve in order to validate this experiment.

Analysis and expression of results

The specific radioligand binding of each receptor was defined as the difference between total binding and nonspecific binding determined in the presence of an excess of unlabeled ligand. Mean values, expressed as a percentage of inhibition of specific binding, are presented in Table 5. IC_{50} values (concentration required to inhibit 50% of specific binding) were determined by non linear regression analysis of their competition curves. These parameters were obtained by curve fitting using Sigmaplot™ software.

Table 5

Binding of R-oxybutynin and S-oxybutynin to calcium channels
[Inhibition (in %) of diltiazem and verapamil binding to calcium channel receptors.]

Receptor	R-OXY (10^{-5}M)	S-OXY (10^{-5}M)	Ref. Compound IC_{50}(nM)
Calcium (diltiazem)	86	59	diltiazem 55.8
Calcium (verapamil)	86	68	D600 36.4

These results indicate that S-OXY has calcium entry blocking activity similar to R-OXY.

ENANTIOMERS OF DESETHYLOXYBUTYNIN

The major metabolite of racemic oxybutynin is RS-desethyloxybutynin (DEO). Prior to our studies, the R and S enantiomers of DEO had not been described, and the antispasmodic and calcium entry blocking activities of the individual enantiomers, R- and S-DEO were unknown. We have synthesized these enantiomers and have studied their antimuscarinic, spasmolytic and calcium entry blocking effects in models of receptor binding and bladder function. We have found that each enantiomer of the metabolite retains the relative pharmacological profile of its "parent" oxybutynin enantiomer.

Binding at Muscarinic Receptor Subtypes

The percent inhibition of specific radioligand binding induced by three concentrations of each compound (R-, S-, and RS-DEO) was tested at cloned human muscarinic receptor subtypes (M1-M4), as described above for the enantiomers of oxybutynin. The tables below (Tables 6 and 7) give the percent inhibition at each subtype. In addition, IC_{50} values were determined for M_1 and M_2 human receptor subtypes and are presented in Table 6.

Table 6

	M_{1H}				M_{2H}			
	10^{-9}M	10^{-7}M	10^{-5}M	IC_{50} (nM)	10^{-9}M	10^{-7}M	10^{-5}M	IC_{50} (nM)
R-DEO	63	100	100	1.2	21	97	102	14.7
S-DEO	--	82	101	25.4	--	36	101	177
RS-DEO	43	100	100	1.8	--	94	99	7.0

Table 7

	M_{3H}			M_{4H}		
	10^{-9}M	10^{-7}M	10^{-5}M	10^{-9}M	10^{-7}M	10^{-5}M
R-DEO	58	100	100	58	100	99
S-DEO	--	63	99	--	43	99
RS-DEO	36	99	101	34	99	95

These results indicate that S-DEO has less affinity for muscarinic receptor subtypes than either R- or racemic DEO.

Binding at Calcium Channels

The percent inhibition of specific radioligand binding induced by each compound (R-, S-, and RS-DEO) was tested at the diltiazem and verapamil sites of the L-type calcium channel. The results are shown in Table 8.

Table 8

Receptor	R-Deo 10^{-5}M	S-DEO 10^{-5}M	RS-DEO 10^{-5}M
Calcium (diltiazem)	86	72	88
Calcium (verapamil)	96	76	89

These results indicate that S-DEO has calcium entry blocking activity similar to that of R- and racemic DEO.

Functional Characterization of Antimuscarinic/ Antispasmodic Activity

The effects of R-, S- and RS-Oxybutynin (OXY) and of R-, S-, and RS-DEO were studied in an in vitro model of bladder function. As described below, isolated strips of guinea pig bladder smooth muscle were mounted in a tissue bath and contracted either with the muscarinic agonist carbachol or with increasing concentrations of external potassium.

Bladder strips. Experiments were performed using methods similar to those described by Kachur et al, 1988 and Noronha-Blob and Kachur, 1991. Strips of tissue (approximately 10 mm long and 1.5 mm wide) were removed from the body of the urinary bladder of male Hartley guinea pigs weighing 400-600 g. (Elm Hill Breeding Laboratories, Chelmsford, MA). The tissues were suspended in an oxygenated buffer of the following composition, in mM: NaCl, 133; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 0.6; NaH_2PO_4, 1.3; $NaHCO_3$, 16.3; and glucose, 7.7. They were maintained at 37.5° C. Contractions were recorded with isometric transducers (Model FT-10) and an ink-writing polygraph (Model 7) (Astro-Med, Inc., Grass Instrument Div., West Warwick, RI). A resting tension of 0.5 grams was maintained on all tissues at all times.

In each experiment up to seven strips were removed from a single bladder, suspended in individual tissue chambers and allowed to equilibrate with the bathing solution for one hour before proceeding with the experiment.

Carbachol-induced contractions. One series of experiments focused on the anticholinergic actions of oxybutynin. In these experiments, in order to assess the viability of each tissue and to serve as a frame of reference, contractions of each strip of tissue were recorded initially in response to exposure to tissue medium in which the NaCl was replaced by KCl to yield a concentration of 137.7 mM KCl in the medium. This was followed by return to the standard medium, and then by exposures to progressively increasing concentrations of carbachol, with separate exposures to each concentration only until the peak response had been recorded. Then, leaving one strip untreated and/or one strip exposed to 17 mM ethanol to serve as control tissue(s), the remaining strips each were exposed for one hour to one concentration of an antagonist. The ethanol controls were used when, because of poor solubility, stock solutions of test substances had to be prepared in ethanol, as a result of which the tissue baths experienced an effective

concentration of 17 mM ethanol. Finally, the responses to increasing concentrations of carbachol followed by exposure to 137.7 mM KCl were recorded a second time.

Potassium-induced contractions. A second series of experiments focused on the spasmolytic action of the substances being studied. Contractions were recorded in response to sequentially increasing the concentration of potassium in the medium.

Data analysis. To determine whether antagonists decreased the peak response to agonists, the peak tension developed by each strip during the second set of determinations was expressed as a percent of the peak tension developed during the first concentration-effect determination. Then, for each antagonist the resultant data were analyzed for treatment-related differences by one-way analysis of variance (ANOVA). Since only one concentration of antagonist was studied in each strip of bladder, the procedures of Arunlakshana and Schild (1959) were used in modified form to estimate the pA2 and slope of the Schild regression. First, the concentrations of agonist producing a half-maximal response (the EC_{50}) was estimated for each strip from the second set of concentration-effect data. The EC_{50} was obtained from linear regression lines fit to the logarithm of the concentration of drug and the responses bracketing the half maximum level of response. For each drug-treated strip, a "concentration ratio" (CR) was calculated as the ratio of the EC_{50} of the treated tissue divided by the EC_{50} of the untreated tissue. For each experiment where two or more strips were exposed to the same chemical but at different concentrations, the logarithm of this ratio minus one [i.e., log (CR-1)] was plotted against the logarithm of the concentration of antagonist to which the strip had been exposed to produce "Schild plots". A regression analysis relating log(CR-1) to the logarithm of the concentration of the antagonist was employed to estimate the pA2 and the slope of the regression line. Finally, experiments were grouped by chemical and the mean $\pm$ S.E. of the pA2 and slope were calculated. The 95% confidence limits (CL) for the slope were estimated from its S.E. using standard methods. For experiments in which only one strip was exposed to a given chemical, a pKD was calculated as (concentration of antagonist)/(CR-1) and the negative logarithm of the KD was then pooled with the pA2 values to yield an expanded set of pA2 values.

The effects of racemic oxybutynin and DEO and their respective enantiomers on carbachol-induced contraction are summarized in Table 9 below. Values given are the

summary of Schild analyses which gives pA2 values [mean ± SE] and slope [mean ± SE].

Table 9

Antagonist	No. of expts.	pA2	Slope
R-OXY	4	8.80 ± 0.27	1.28 ± 0.26
S-OXY	4	7.09 ± 0.13	1.13 ± 0.17
RS-OXY	5	8.81 ± 0.29	1.34 ± 0.15
R-DEO	4	9.04 ± 0.32	1.16 ± 0.11
S-DEO	4	7.31 ± 0.35	0.87 ± 0.11
RS-DEO	4	8.55 ± 0.32	1.35 ± 0.25

These results indicate that both S-OXY and S-DEO are less potent antagonists of bladder muscarinic receptors than are R- and racemic OXY and R- and racemic DEO.

The effects of racemic oxybutynin and its enantiomers on potassium-induced contraction are summarized in Table 10 below. (Values given are the magnitude of contraction induced by 137.7 mM K+ after 60 min exposure to compound divided by the magnitude of contraction induced before exposure to drug.)

Table 10

Antagonist	Mean % pretreatment ± SE (n=3)
R-OXY	32 ± 8*
S-OXY	26 ± 9*
RS-OXY	20 ± 1*
R-DEO	36 ± 5*
S-DEO	42 ± 5*
RS-DEO	47 ± 8*

*Significantly different from corresponding value for untreated tissues ($p<0.01$)

These results indicate that oxybutynin and its enantiomers and desethyloxybutynin and its enantiomers are equipotent as bladder smooth muscle spasmolytics.

While it is well known that the normal emptying of the bladder is mediated through cholinergic mechanisms, the bladder instability that is seen in patients suffering

from incontinence appears to be related to non-cholinergic contractions of the bladder. Andersson et al. [Neurourol Urodyn 5, 579-586 (1986)] have shown in animals that the atropine-resistant detrusor muscle is highly sensitive to calcium antagonists.

The study of the receptor binding affinities of (R)- and (S)-oxybutynin to the receptor sites for the calcium channel blockers diltiazem and verapamil described above allows one to conclude that S-oxybutynin and (S)-desethyloxybutynin have therapeutic effects on involuntary micturition, while (unlike the R-isomers and the racemates) having very little effect on the normal voiding mechanism. Both S-OXY and S-DEO also exhibit significantly decreased anticholinergic side effects as compared with the corresponding R-isomer and racemate. The avoidance of cardiovascular side effects that arise from the anticholinergic action of racemic oxybutynin is of particular note. We conclude that S-oxybutynin and S-desethyl oxybutynin are effective medicaments for the treatment of urinary incontinence in humans with greatly reduced side effects over the racemates or the pure R-enantiomers.

EXAMPLES

Example 1
ORAL FORMULATION

Capsules:

Formula	Quantity per capsule in mg		
	A	B	C
S-DEO	50	100	200
Lactose	230	280	330
Cornstarch	65	65	65
Magnesium Stearate	5	5	5
Compression Weight	350	450	600

The S-DEO, lactose and cornstarch are blended until uniform and then the magnesium stearate is blended into the resulting powder, which is sieved and filled into suitably sized, two-piece, hard gelatin capsules using conventional machinery. Other doses may be prepared by altering the fill weight and, if necessary, changing the capsule size to suit.

Since at least one crystalline form of the compounds of the invention is needle-like, it is desirable to mill or granulate the active ingredient to provide a free-flowing powder for tabletting or encapsulation, when employing dry-powder techniques.

Example 2

ORAL FORMULATION

Tablets:

Formula	Quantity per tablet in mg		
	A	B	C
S-OXY	50	100	200
Lactose	205	245	245
Cornstarch	30	50	50
Water (per thousand Tablets)*	300 mL	500 mL	500 mL
Cornstarch	60	100	100
Magnesium Stearate	5	5	5
Compression Weight	350	500	600

*The water evaporates during manufacture

The S-OXY is blended with the lactose until a uniform blend is formed. The smaller quantity of cornstarch is blended with the water to form the resulting corn starch paste. This is then mixed with the uniform blend until a uniform wet mass is formed. The remaining cornstarch is added to the resulting wet mass and mixed until uniform granules

are obtained. The granules are then screened through a suitable milling machine, using a 1/4 inch stainless steel screen. The milled granules are dried in a suitable drying oven until the desired moisture content is obtained. The dried granules are then milled through a suitable milling machine, magnesium stearate is blended in, and the resulting mixture is compressed into tablets of the desired shape, thickness, hardness and disintegration. Tablets of other strengths may be prepared by altering the ratio of active ingredient to the excipients or to the final weight of the tablet.

CLAIMS

We claim:

1. A method for treating urinary incontinence while avoiding concomitant liability of adverse effects, which comprises administering to a mammal in need of such treatment from about 100 mg to about 1 gram per day of a compound chosen from the group consisting of (S)-oxybutynin, (S)-desethyloxybutynin or a pharmaceutically acceptable salt of either, substantially free of its (R) enantiomer.

2. The method according to claim 1, wherein the amount of (S)-oxybutynin, (S)-desethyloxybutynin, or a pharmaceutically acceptable salt of either, administered is from about 240 mg to about 750 mg per day.

3. The method according to claim 2, wherein the amount of (S)-oxybutynin, (S)-desethyloxybutynin, or a pharmaceutically acceptable salt of either, administered is from about 300 mg to about 600 mg per day.

4. The method according to claim 1, wherein (S)-oxybutynin, (S)-desethyloxybutynin, or a pharmaceutically acceptable salt of either, is administered parenterally, transdermally, rectally, orally or by inhalation.

5. The method according to claim 4, wherein (S)-oxybutynin, (S)-desethyloxybutynin, or a pharmaceutically acceptable salt of either, is administered orally or transdermally.

6. A pharmaceutical unit dosage form in the form of a tablet or a soft elastic gelatin capsule which comprises a pharmaceutically acceptable carrier and from 0.1 to 500 mg of one of the group consisting of (S)-oxybutynin, (S)-desethyloxybutynin, or a pharmaceutically acceptable salt of either, substantially free of its (R) enantiomer.

7. The pharmaceutical unit dosage form according to claim 6, wherein (S)-oxybutynin, (S)-desethyloxybutynin, or a pharmaceutically acceptable salt of either is present in an amount of about 25 mg to about 250 mg.

8. The pharmaceutical unit dosage form according to claim 7, wherein (S)-oxybutynin, (S)-desethyloxybutynin, or a pharmaceutically acceptable salt of either, is present in an amount of about 100 mg to about 200 mg.

9. A pharmaceutical dosage form in the form of a transdermal delivery device which comprises a pharmaceutically acceptable carrier and from 0.1 to 500 mg of one of the group consisting of (S)-oxybutynin, (S)-desethyloxybutynin, or a pharmaceutically acceptable salt of either, substantially free of its (R) enantiomer.

10. The pharmaceutical dosage form according to claim 11 wherein said pharmaceutically acceptable carrier comprises a permeation enhancer.

INTERNATIONAL SEARCH REPORT

Interr. ial Application No
PCT/US 97/11570

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/215

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 96 23492 A (SEPRACOR INC.) 8 August 1996 cited in the application see claims 1-16 ---	1-10
P,X	US 5 532 278 A (G. ABERG ET AL) 2 July 1996 see claims 1-9 see column 4, line 27 - line 42 & WO 96 23492 A cited in the application ---	1-10
X	WO 95 09007 A (ALZA CO.) 6 April 1995 see page 16, line 18 - line 23 see page 20, line 14 - line 22 see page 30; table 4 see claims 1,30,42,46 --- -/--	1,4,5,9, 10

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
15 October 1997	28. 10. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Siatou, E

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INTERNATIONAL SEARCH REPORT

Inte. ..nal Application No
PCT/US 97/11570

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 12, no. 155 (C-494), 12 May 1988 & JP 62 267224 A (KODAMA KK), 19 November 1987, see abstract	1-10
A	L. NORONHA-BLOB ET AL: "Enantiomers of Oxybutynin: In Vitro Pharmacological Characterization at M1, M2 and M3 Muscarinic Receptors and in Vivo Effects on Urinary Bladder Contraction, Mydriasis and Salivary Secretion in Guinea Pigs" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 256, no. 2, February 1991, USA, pages 562-567, XP000572006 cited in the application see abstract	1-10
A	J. F. KACHUR ET AL: "R and S Enantiomers of Oxybutynin: Pharmacological Effects in Guinea Pig Bladder and Intestine" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 247, no. 3, December 1988, USA, pages 867-872, XP000572052 cited in the application see abstract	1-10

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inter. nal Application No
PCT/US 97/11570

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		AU 4966496 A	21-08-96
		NO 973516 A	07-08-97
US 5532278 A	02-07-96	AU 4966496 A	21-08-96
		NO 973516 A	07-08-97
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		JP 9505279 T	27-05-97
		NZ 274711 A	26-11-96
		NZ 275615 A	26-11-96
		WO 9509006 A	06-04-95

WO9949844

Publication Title:

METHOD FOR PRODUCING TRANSDERMAL THERAPEUTIC SYSTEMS BY USING BASIC ALKALI METAL SALTS FOR CONVERTING ACTIVE AGENT SALTS INTO FREE BASES

Abstract:

Abstract of WO9949844

The invention relates to a method for producing transdermal systems with free active agent bases. The invention is characterized in that, during the production of the system, the free active agent bases are released from active agent salts by reaction with a basic alkali metal salt. Data supplied from the esp@cenet database - Worldwide

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